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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/820,777	04/09/2004	Winston T.K. Cheng	MR2723-365	8832

4586 7590 01/12/2006

ROSENBERG, KLEIN & LEE
3458 ELLICOTT CENTER DRIVE-SUITE 101
ELLICOTT CITY, MD 21043

EXAMINER	
DOWELL, PAUL THOMAS	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/820,777	CHENG ET AL.	
	Examiner	Art Unit	
	Paul Dowell	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-17 are pending.

Specification

The amendment filed 8/30/2004 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: SEQ ID NO:13, SEQ ID NO:14 and SEQ ID NO:15 are disclosed as amino acid sequences in the specification as originally filed on 4/9/2004. The sequence listing filed 8/30/2004 discloses SEQ ID NO:13, SEQ ID NO:14 and SEQ ID NO:15 as nucleic acid sequences. It is noted that Applicant's remarks of 8/30/2004 acknowledge that SEQ ID NO:15 was originally filed as an amino acid sequence but later filed as a nucleic acid sequence in the sequence listing of 8/30/2004. Applicant states in said remarks that the two formats of SEQ ID NO:15 are equivalent (i.e. the nucleic acid sequence of one format encodes the amino acid sequence format of the other). However, this does not appear to be the case because, for example, the originally file amino acid sequence of SEQ ID NO:15 begins with Met as the first amino acid while the first triplet codon of the nucleic acid of SEQ ID NO:15 in the sequence listing appears to be "gcc" which codes for Ala, not Met. Further, no explanation is provided for the new matter introduced related to SEQ ID NO:13 or SEQ ID NO:14. Applicant is required to cancel the new matter in the reply to this Office Action.

The sequence listing of 8/30/2004 identifies the nucleic acids of SEQ ID NO:1 and SEQ ID NO:2 as being of human origin. However, the language of claims 5 and 6 appears to indicate that said nucleic acids are of bovine origin. Clarification is requested.

The disclosure is objected to because of the following informalities: the disclosure is replete with typos, grammatical errors and unclear language. For example: page 9, line 6 recites, "The invention relates to transgenic milk that can be used to produce therapeutical recombinant hFVIII for hemophilia patent treatment."; page 7, line 23 recites "protein in milks was collected"; page 9, line 6 recites "transgenic milk" which apparently should read --milk of/from transgenic animals-- because it is unclear how a fluid not comprising genetic material, such as milk, can be transgenic; page 20, line 14 recites "hybride pigs" which apparently should read --hybrid pigs--; page 27, line 17 recites "Biological active recombinant hFVIII protein derived from transgenic milks is easily collected by diary automatic milk collection system and simply purified procedure to obtain the massive recombinant proteins". Applicants are urged to review and correct the disclosure for additional typos, grammatical errors and unclear language. Appropriate correction is required.

Claim Objections

Claims 2, 5, 6, 11, 12, 15 and 17 are objected to because of the following informalities:

Claim 2 is objected to because it is unclear as to what "why acidic protein" is referring.

Claims 5 and 6 are objected to because of apparent grammatical errors in reciting, "...SEQ ID NO:1/2 which obtained from the...".

Claim 11 is objected to because of an apparent grammatical error in reciting, "...wherein said the mammary gland-specific signal peptide sequences...".

Claim 12 is objected to because of an apparent typo in reciting "he transgenic animal...".

Claim 12 is objected to as being generally incomprehensible in reciting, "...that said created junctional amino acid sequence flanking in Ser-Leu.".

Claim 13 is objected to as being generally incomprehensible in reciting, "...a mature polypeptide which intact human FVIII...".

Claim 17 is objected to as being generally incomprehensible in reciting, "...wherein the purified human FVIII from the transgenic milk can be applied for supplementary therapy used.".

Applicant is urged to thoroughly review the claims for additional typos and unclear language. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 4, 7 and 8 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-9 of copending Application No. 10/727,145 ('145). Although the conflicting claims are not identical, they are not patentably distinct from each other because each are generally drawn to a transgenic animal whose genome comprises a mammary-specific nucleic acid expression cassette comprising a nucleic acid encoding a foreign polypeptide. Claims 1, 2, 4, 7 and 8 of the instant application are drawn to a transgenic animal whose genome comprises said expression cassette comprising a nucleic acid encoding a generic foreign protein. Claims 6-9 of '145 are drawn to a transgenic animal whose genome comprises said expression cassette comprising a nucleic acid encoding hirudin. Thus, claims 6-9 of '145 are entirely encompassed by claims 1, 2, 4, 7 and 8 of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-7 and 9-17 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 1 and 13 are drawn to a transgenic animal and a method of making said transgenic animal. Dependent claim 8 appears to further limit said transgenic animal to mouse, goat or pig. However, it is noted that claim 8 as drafted literally further limits the regulatory element of a gene encoding a milk protein of a mammal since this is the first recitation of "mammal" in claim 1. For the purposes of examination, Examiner has interpreted claim 8 to further limit the transgenic animal of claim 1 to mouse, goat or pig and as such, claim 8 is not included in the instant rejection. However, dependent claims 2-7, 9-12 and 14-17 do not further limit the transgenic animal of claims 1 and 13. Thus, the breadth of claims 1-7 and 9-17 is such that they read on transgenic humans. Humans are considered non-statutory subject matter and as such provides the basis for the instant rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 9-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A non-human transgenic animal whose genome comprises a mammary-specific nucleic acid expression cassette, wherein said mammary-specific nucleic acid expression cassette encodes a human FVIII protein or B-domain deleted human FVIII protein, wherein said human FVIII protein or B-domain deleted human FVIII protein is secreted in milk when said non-human transgenic animal is lactating, wherein said non-human transgenic animal is selected from the group consisting of mouse, goat, pig, sheep and rabbit; and a method of making said non-human transgenic animal,

does not reasonably provide enablement for:

Any transgenic animal whose genome comprises a mammary-specific nucleic acid expression cassette, wherein said mammary-specific nucleic acid expression cassette encodes a human FVIII protein or B-domain deleted human FVIII protein, wherein said human FVIII protein or B-domain deleted human FVIII protein is secreted in milk when said any transgenic animal is lactating; and a method of making said any transgenic animal.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use

the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Independent claim 1 is drawn to a transgenic animal whose genome comprises a mammary-specific nucleic acid expression cassette, said mammary-specific nucleic acid expression cassette comprising: (a) a nucleic acid encoding a polypeptide, (b) a nucleic acid encoding a secretion signal that is operably linked to (a), (c) a nucleic acid polyadenylation signal that is operably linked to (a), and (d) a nucleic acid regulatory element from a gene that is specifically expressed in lactating mammary gland and operably linked to (a), wherein the protein encoded by (a) is secreted in milk. Dependent claims 3, 9, 10 and 12 further limit (a) of claim 1 to nucleic acids encoding human FVIII proteins; dependent claims 4-6, 9 and 11 further limit (b) of claim 1 to

nucleic acids encoding mammary gland-specific secretion signal peptides, wherein said signal peptides are from alpha-lactalbumin or alpha-S1 casein; dependent claim 7 further limites (c) of claim 1 to a nucleic acid comprising a bovine growth hormone polyadenylation signal; dependent claim 2 further limits (d) of claim 1 to nucleic acids that are regulatory elements from the genes encoding alpha-lactalbumin, beta-lactoglobulin, whey acidic protein and casein; and dependent claim 8 further limits the transgenic animal of claim 1 to mouse, goat or pig. Claims 13-17 are drawn to a method of making the transgenic animal of claim 1.

The specification discloses a variety of mammary gland-specific promoters that were known at the time of the invention and that drive expression of genes whose protein products are secreted into milk (page 9, lines 21 to page 10, line 20). The specification also discloses a variety of signal peptide sequences that were known at the time of the invention and that function to promote secretion of milk proteins into milk (page 10, line 21 to page 11, line 4). The specification discloses nucleic acid constructs encoding human FVIII proteins, production of transgenic animals whose genomes comprise said nucleic acid constructs and analysis of said transgenic animals for recombinant production of human FVIII proteins secreted in the milk of said transgenic animals (page 11, line 5 to page 16, line 23). Working examples 1-5 disclose generation of transgenic animals (mice, pigs and goats) carrying the disclosed nucleic acid constructs, expression pattern of the genes encoding human FVIII proteins (hFVIII) in said transgenic animals, expression and secretion of recombinant hFVIII proteins in the

milk of said transgenic animals and analysis of the clotting activity of said recombinant hFVIII proteins (page 19, line 10 to page 25, line 18).

Claim 1 is drawn to a transgenic animal whose genome comprises a mammary-specific nucleic acid expression cassette. Claim 13 is drawn to a method of producing the transgenic animal of claim 1. The breadth of claims 1 and 13 is such that they read on any transgenic animal including humans and whales, for example, in addition to mice, goats, pigs, sheep and rabbits. Neither the specification nor the art of record at the time of the invention provide sufficient guidance to allow an artisan to make the instant invention commensurate in scope with the breadth of these claims. Teachings of transgenic humans or whales, for example, are non-existent. Further, the art of record at the time of the invention teaches the unpredictability of producing transgenic animals by microinjecting nucleic acid targeting vectors into early stage embryos. For example, Niemann et al **(Animal Reproduction Science, 79:291-317, 2003)** teaches that microninjection into pronuclei of zygotes is inefficient, results in random integration into the host genome and variable expression of the introduced transgene due to position effects (page 294, paragr. 2). Further, Houdebine et al **(Transgenic Research, 9:305-320, 2000)** teaches that: "Numerous experiments have shown that the level and specificity of expression of a gene construct used as a transgene cannot be easily predicted. DNA addition by microinjection generates lines of animals expressing the foreign gene at quite different levels. It is admitted that this phenomenon is due to a large extent to a position effect." (page 309, col. 2, paragr. 3, line 1 to page 310, col. 1, line 2). However, the art of record at the time of the invention teaches transgenic mice

(Chen et al, Transgenic Research, 11:257-268, 2002), sheep **(Niemann et al, Transgenic Research, 8:237-247, 1999)**, pigs **(Paleyanda et al, Nature Biotechnology, 15:971-975, 1997)** and rabbits **(Hiripi et al, DNA and Cell Biology, 22:41-45, 2003)** that express transgenically introduced genes encoding FVIII and the specification teaches transgenic mice, goats and pigs that express transgenically introduced genes encoding FVIII proteins. Thus, while the state of the art of producing transgenic animals by microinjection of nucleic acid constructs into pronuclei early stage embryos was unpredictable at the time of the invention, the instant claims are enabled for transgenic mice, goats, pigs, sheep and rabbits that express transgenically introduced FVIII and a method of producing these transgenic animals. However, an artisan would experience undue experimentation to make any transgenic animals expressing an introduced FVIII gene because of the unpredictable state of the art of producing transgenic animals by microinjection of nucleic acid constructs into pronuclei early stage embryos at the time of the invention.

In summary, an artisan of skill would have required extensive experimentation to practice the claimed invention commensurate in scope with the instant claims. Such experimentation will be undue because of the unpredictability of making any transgenic animal expressing an introduced FVIII gene. Neither the specification nor the art of record at the time of the invention provides sufficient guidance to address these issues for an artisan to practice the claimed invention.

Thus, limiting the scope of the claims to:

A non-human transgenic animal whose genome comprises a mammary-specific nucleic acid expression cassette, wherein said mammary-specific nucleic acid expression cassette encodes a human FVIII protein or B-domain deleted human FVIII protein, wherein said human FVIII protein or B-domain deleted human FVIII protein is secreted in milk when said non-human transgenic animal is lactating, wherein said non-human transgenic animal is selected from the group consisting of mouse, goat, pig, sheep and rabbits; and a method of making said non-human transgenic animal, is proper.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "A transgenic animal whose genome comprises a mammary-specific expression cassette, said expression cassette system comprising..." in lines 1-2. There is a preceding recitation of an *expression cassette* but there is no preceding recitation of an *expression cassette system*. It is unclear if Applicant is referring to the same thing.

Step (d) of claim 1 recites:

> "a regulatory element of a gene encoding a milk protein of a ***mammal*** operably linked to the DNA sequences of (a), (b) and (c) above so as to form a hybrid gene which is expressible in the mammary gland of an adult lactating female of a transgenic animal whose genome comprises said hybrid gene; so that the mature

polypeptide is secreted at detectable levels into the milk of said ***mammal*** if said ***mammal*** is a lactating female."

Claim 8 recites, "The transgenic animal according to claim 1, wherein ***the mammal*** is selected from the group consisting of mouse, goat and pig species." Examiner believes Applicants intend claim 8 to read, --The transgenic animal according to claim 1, wherein the ***transgenic animal*** is selected from the group consisting of mouse, goat and pig species--. Claim 8 as drafted by Applicant further limits the animal source genome (i.e. from mouse, goat or pig) of a regulatory element of a gene encoding a milk protein of a ***mammal***, and does not clearly further limit the transgenic animal of claim 1.

Claim 1 recites "said mammary gland cells" in line 8, however, there is no preceding recitation of mammary gland cells in claim 1. There is insufficient antecedent basis for this recitation in the claim.

Claim 1 recites "signal sequence preceding and operably linked to downstream of (a)" in lines 9-10. The instant recitation is generally confusing as it is unclear how a signal sequence could be both preceding (i.e. placed before (a)) and operably linked downstream (i.e. placed after (a)).

Claims 4, 5 and 6 depend from claim 1 and recite "the signal peptide" in line 2 of said claims. However, claim 1 contains no recitation of a signal peptide. There is insufficient antecedent basis for this recitation in the claims.

Claim 9 depends from claim 3 and rectites, "wherein said nucleotide sequence" in lines 1-2. However, claim 3 contains no recitation of a nucleotide sequence. There is insufficient antecedent basis for this recitation in the claim.

Claim 15 is generally incomprehensible in reciting, "...at least two different mature polypeptides which intact human FVIII and B domain-deleted human FVIII.". It is noted that for the purposes of examination claim 15 is interpreted to read as follows: The method for producing the transgenic animal according to claim 13, wherein a plurality of different expression cassettes are introduced and these cassettes express at least two different mature human FVIII or B-domain deleted human FVIII polypeptides.

Claim 16 recites "its clotting activity" in line 2. It is unclear as to what "its" refers (e.g. human FVIII protein contained within the milk, the milk or transgenic animals).

Claim 17 depends from claim 13 and recites "the transgenic milk" in lines 1-2. However, claim 13 contains no recitation of transgenic milk. There is unsufficient antecedent basis for this limitation in the claim. Further, the meaning of the term "transgenic milk" is unclear.

In addition to the specific reasons put forth herein above, claims 2-17 depend from claim 1 and are likewise rejected. Applicants are urged to thoroughly review the claims for additional typos and grammatical inconsistencies.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent

granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 8, 10, 12, 13, 14 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Lubon et al **(US Patent 6,255,554, Issued July 3, 2001)**.

Lubon teaches a non-human transgenic animal that expresses hFVIII protein or a fragment thereof as a secretion product in milk (claim 1) and a method of making said transgenic animal (claim 28). Lubon teaches a nucleic acid construct with which said transgenic animal was constructed comprising a nucleic acid encoding hFVIII (claims 1, 4 and 5, for example), a nucleic acid from the mouse whey acidic protein (WAP) gene polyadenylation signal (claim 12), a nucleic acid from the mouse WAP gene promoter that drives mammary gland-specific gene expression (claim 3) and a nucleic acid encoding a secretion signal peptide from milk proteins, specifically the secretion signal peptide from WAP (col. 6, lines 45-56). Lubon teaches a method of making said transgenic animal comprising introducing said nucleic acid construct into a non-human mammalian embryo and permitting the embryo to develop into a non-human transgenic animal (claim 28). Thus, Lubon anticipates the instant claims.

Claims 1-3, 8, 13, 14 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Paleyanda et al **(Nature Biotechnology, 15:971-975, 1997)**.

Paleyanda teaches a transgenic pig that expresses full length hFVIII protein as a secretion product in milk and a method of making said transgenic pig. Paleyanda

teaches a nucleic acid construct with which said transgenic pig was constructed comprising a nucleic acid encoding hFVIII, a nucleic acid from the mouse WAP gene polyadenylation signal and a nucleic acid from the mouse WAP gene promoter that drives mammary gland-specific gene expression (see entire document and particularly page 974, col. 2, paragr. 2). Paleyanda teaches a method of making said transgenic pig comprising microinjecting said nucleic acid construct into porcine embryos and transferring the microinjected embryos into recipient sows (page 972, col. 1, lines 1-3). Paleyanda teaches that said method results in the production of a transgenic pig that secretes 1.0-2.7 μg/ml hFVIII with a clotting activity of 0.42-0.62 U/ml active hFVIII protein (page 974, col. 1, paragr. 5, lines 2-4). It is noted to Applicant that:

> When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent. See MPEP 2112.01 and *In re Best,* 195 USPQ 430, 433 (CCPA 1997). The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989).

In the instant case, the recombinant hFVIII protein secreted in the milk of the transgenic pig taught by Paleyanda clearly contained a signal sequence encoding a secretional peptide because the recombinant hFVIII protein was secreted in the milk of said transgenic pig. Thus, Paleyanda anticipates the instant claims.

Claims 1-5, 7-9, 11, 13, 14, 16 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al **(Transgenic Research, 11:257-268, 2002)**.

Chen teaches a transgenic mouse that expresses full length hFVIII protein as a secretion product in milk and a method of making said transgenic mouse. Chen teaches a nucleic acid construct with which said transgenic mouse was constructed comprising a nucleic acid encoding hFVIII, a nucleic acid encoding the secretion signal peptide from the alpha-lactalbumin gene, a nucleic acid from the bovine growth hormone gene polyadenlyation signal and a nucleic acid from the bovine alpha lactalbumin gene promoter that drives mammary gland-specific gene expression (page 258, col. 2, paragr. 2 to page 259, col. 1, line 18 and page 264, col. 2, paragr. 1, lines 10-14). Chen teaches a method of making said transgenic mouse by microinjecting said nucleic acid construct into pronuclei of fertilized eggs from super ovulated female mice of the outbred ICR strain and then transferring the microinjected eggs to recipient pseudopregnant female mice (page 259, col. 1, paragr. 1, lines 1-5). Chen teaches that said method results in the production of transgenic mice whose genomes contain low (1-5 copies) and high (40-50 copies) numbers of copies of the nucleic acid construct (page 262, col. 1, lines 3-11). Chen teaches that the milk from the resultant lactating transgenic mice contained 7.0-50.2 μg/ml hFVIII protein (page 263, col. 2, paragr. 2, lines 1-4 and see Table 2) and that said hFVIII protein exhibited a clotting activity 13-fold greater than the clotting activity of normal human plasma (page 264, col. 1, paragr. 1, lines 8-9 and see Table 2). Thus, Chen anticipates the instant claims.

Claims 1, 2, 4, 7, and 8 are provisionally rejected under 35 U.S.C. 102(e) as being anticipated by copending Application No. 10/727,145 ('145) which has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e), if published under 35 U.S.C. 122(b) or patented. This provisional rejection under 35 U.S.C. 102(e) is based upon a presumption of future publication or patenting of the copending application.

Claims 1, 2, 4, 7 and 8 of the instant application are drawn to a transgenic animal whose genome comprises a mammary-specific nucleic acid expression cassette comprising a nucleic acid encoding a generic foreign protein. Claims 6-9 of '145 are drawn to a transgenic animal whose genome comprises a mammary-specific nucleic acid expression cassette comprising a nucleic acid encoding hirudin. Thus, claims 6-9 of '145 anticipate claims 1, 2, 4, 7 and 8 of the instant application.

This provisional rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. This rejection may not be overcome by the filing of a terminal disclaimer. See *In re Bartfeld*, 925 F.2d 1450, 17 USPQ2d 1885 (Fed. Cir. 1991).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6, 10, 12 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al **(Transgenic Research, 11:257-268, 2002)** in view of Soukharev et al **(Blood Cells, Molecules and Diseases, 28:234-248, 2002)**, DeBoer et al **(US Patent 5,633,076, Issued May 27, 1997)** and Lubon **(US Patent 6,255,554, Issued July 3, 2001)**.

Chen teaches a transgenic mouse that expresses full length hFVIII protein as a secretion product in milk and a method of making said transgenic mouse as put forth herein above in the 35 U.S.C. 102(b) rejection. Chen does not teach including nucleic acid encoding bovine alphaS1-casein signal peptide in the nucleic acid construct used to generate the transgenic mouse. Chen does not teach a transgenic animal expressing B-domain deleted hFVIII. Chen does not teach expressing two different FVIII polypeptides in transgenic animals.

Soukharev teaches the state of the art of expressing recombinant hFVIII in the milk of transgenic animals. Soukharev teaches that "another approach to improve recombinant FVIII molecule is to introduce modifications to improve its effective secretion from FVIII-expressing cell" (page 239, col. 1, paragr. 1, lines 1-4). Soukharev teaches that "removal of the B domain...was found to dramatically improve the yield of

FVIII" (page 237, col. 2, lines 3-6). Soukharev teaches that "an attractive possibility to increase the yield of rFVIII is to produce a biologically active form of FVIII by coexpressing its heavy and light chains" (page 239, paragr. 2, line 1 to col. 2, line 2).

DeBoer teaches the state of the art of expressing recombinant proteins in the milk of transgenic animals. DeBoer teaches a nucleic acid construct with which to generate said transgenic animals. De Boer teaches said nucleic acid construct comprising various nucleic acid elements for the optimization of producing recombinant protein in the milk of transgenic animals, said recombinant protein including FVIII (col. 7, line 12). DeBoer teaches said various nucleic acid elements to include a nucleic acid encoding alpha S1 casein secretion signal peptide operably linked to a nucleic acid encoding said recombinant protein specifically for the purpose of promoting secretion of said recombinant protein in the milk of transgenic animals (col. 7, lines 18-27). DeBoer also teaches said various nucleic acid elements to include promoter regions of mammary-gland specific genes such as alpha-lactalbumin, whey acidic protein, beta-casein and alpha S1 casein (col. 2, line 53 to col. 3, line 5).

Lubon teaches a non-human transgenic animal that expresses hFVIII protein or a fragment thereof as a secretion product in milk and a method of making said transgenic animal as put forth herein above in the 35 U.S.C. 102(b) rejection. Lubon recites, "Important to the present invention are regulatory sequences that direct secretion of proteins into milk and/or other body fluids of the transgenic animal. In this regard, both homologous and heterologous regulatory sequences are useful in the invention. Generally, regulatory sequences known to direct the secretion of milk proteins, such as

either signal peptides from milk proteins or the nascent target polypeptide, can be used..." (col. 6, lines 45-52).

It would have been obvious to an ordinary artisan at the time of the invention to modify the hFVIII-expressing transgenic mouse of Chen by: (i) using a nucleic acid construct encoding different secretion signal peptides fused to hFVIII (e.g. the secretion signal peptide encoded by the alphaS1-casein gene or the alpha-lactalbumin gene), (ii) using a B-domain deleted hFVIII construct and (iii) using two different expression cassettes encoding two different hFVIII polypeptides as taught by Soukharev, DeBoer and Lubon with a reasonable expectation of success. Motivation to modify the hFVIII-expressing transgenic mouse of Chen is provided by Soukharev because Soukharev teaches: (i) that introducing modifications to the FVIII molecule will likely improve secretion of FVIII from cells (page 239, col. 1, paragr. 1, lines 1-4), (ii) that removal of the B domain dramatically improves the yield of FVIII (page 237, col. 2, lines 3-6) and (iii) that coexpressing two different forms of FVIII, the heavy and light chains of FVIII, will produce greater yields of biologically active FVIII (page 239, paragr. 2, line 1 to col. 2 line 2). Further, both DeBoer and Lubon provide additional motivation in teaching the variety of well known and interchangeable nucleic acid elements to be used to improve expression levels and increase secretion levels of recombinant proteins produced in the milk of transgenic animals. Still further, Chen provides additional motivation: "Further efforts will focus on optimizing rFVIII production in mammary expression systems by expressing B-domain deleted constructs" (page 267, col. 2, lines 1-3).

Conclusions

No claims are allowed.

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment and provide any statements that might help to identify support for the claimed invention (e.g. if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul Dowell whose telephone number is 571-272-5540. The examiner can normally be reached on M-F, 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Paul Dowell
Art Unit 1632

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER